Paper No. 25

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte FRANK BECHER and THOMAS KISSEL

Appeal No. 1997-2336
Application No. 08/256,065[1]

HEARD JULY 11, 2000

Before WILLIAM F. SMITH, Administrative Patent Judge, McKELVEY, Senior Administrative Patent Judge, and ROBINSON, Administrative Patent Judge.

ROBINSON, Administrative Patent Judge.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 from the final rejection of claims 27 - 36. Claims 19-26 remain pending but are not now subject to rejection or objection.[2]

[1] This application was filed on August 4, 1994 under the provisions of 35 U.S.C. § 371 as a national stage application of PCT/EP92/02914 which was filed December 16, 1992. Therefore, the present application has an effective filing date of December 16, 1992. (35 U.S.C. § 363; 37 CFR § 1.495).

[2] We find no explicit statement by the examiner indicating that claims 19-26 are allowable. We note the examiner's statement, in the Examiner's Answer (Answer) of September 4, 1996 (Paper No. 17), that "The statement of the status of claims contained in the brief is correct. (Answer, page 1). Appellants indicate that "[p]resumably, claims 19-26 therefore will have been found allowable." Therefore, it is our understanding that these claims are not before us.

Claims 27, 30, 35, and 36 are representative of the subject matter on appeal and read as follows:

27. A transdermal therapeutic application system useful for cancer prophylaxis for applying through the skin of a person, an effective cancer prophylactic amount of an active ingredient consisting essentially of

acetyl salicylic acid or a non-toxic pharmaceutically acceptable salt thereof or a combination thereof;

said transdermal therapeutic application system comprising a matrix containing a substance such that hydrolysis of acetyl salicylic acid is precluded or is at least greatly reduced; and

said substance being selected from the group consisting of dioctyl cyclohexane, dioctyl cyclohexane dissolved in n-heptane, glycerol ester of a partially hydrogenated colophonium and dioctyl cyclohexane dissolved in n-heptane, and silicone oil.

30. A therapeutic method for preventing cancer in a person, comprising

administering through a transdermal therapeutic application system applied to the skin of said person,

an effective cancer prophylactic amount of an active ingredient consisting essentially of

acetyl salicylic acid or a non-toxic pharmaceutically acceptable salt thereof or a combination thereof; and

said transdermal application system comprising a matrix containing a substance such that hydrolysis of acetyl salicylic acid is precluded or is at least greatly reduced;(sic, .)

35. The therapeutic method of claim 30,

wherein said cancer prophylaxis is against tumor formation.

36. The therapeutic method of claim 35,

wherein said tumor formation prophylaxis is in the gastrointestinal tract.

There are no references relied upon by the examiner in this appeal.

The following references are relied upon by appellants:

Thun et al. (Thun I), "Aspirin Use and Reduced Risk of Fatal Colon Cancer," New England Journal of Medicine, Vol. 325, pp. 1593-96 (1991)

Gridley et al. (Gridley), "Incidence of Cancer Among Patients With Rheumatoid Arthritis," Journal of the National Cancer Institute, Vol. 85, No. 4, pp. 307-311 (1993)

Thun et al., "Aspirin Use and Risk of Fatal Cancer," Cancer Research, Vol. 53, pp. 1322-1327 (1993)

Kelloff et al. (Kelloff I), "Chemopreventive Drug Development: Perspectives and Progress," Cancer Epidemiology, Biomarkers & Prevention, Vol. 3, pp. 85-98 (1994)

Kelloff et al. (Kelloff II), "Strategy and Planning for Chemopreventive Drug Development: Clinical Development Plans," Journal of Cellular Biochemistry, Supplement, Vol. 20, pp. 55-62 (1994)

Morgan et al. (Morgan), "NSAIDs and the Chemoprevention of Esophageal Cancer," The Lancet, Vol. 343, pp. 176-177 (1994)

Paganini-Hill, "Aspirin and the Prevention of Colorectal Cancer: A Review of the Evidence," Seminars in Surgical Oncology, Vol. 10, pp. 158-164 (1994)

Schreinemachers et al. (Schreinemachers), "Aspirin Use and Lung, Colon, and Breast Cancer Incidence in a Prospective Study," Epidemiology, Vol. 5, No. 2, pp. 138-146 (1994)

Baron et al. (Baron), "A Broad Anticancer Effect of Aspirin?", Epidemiology, Vol. 5, No. 2, pp. 133-135 ((March 1994)

Baron, "Aspirin and Cancer," Preventive Medicine, Vol. 24, pp. 121-124 (1995)

Morgan, "NSAIDs and the Chemoprevention of Colon and Esophageal Cancer," Gut, Vol. 36, pp. 153-154 (1995)

Stellman, "Aspirin and Cancer: Report on an American Health Foundation Workshop," Preventive Medicine, Vol. 24, pp. 101-102 (1995)

Castleman, “The 2-cent Miracle Medicine that Fights Heart Disease, Cancer, and more," Family Circle, Vol. 108, No. 3, p. 20 (Feb. 21, 1995)

Nelson, “Aspirin Prevention Update: New Data on Lung and Colon Cancers,” Journal of the National Cancer Institute, Vol. 87, No. 8, pp. 567-569 (April 19, 1995)

Giovannucci et al. (Giovannucci), “Aspirin and the Risk of Colorectal Cancer in Women,” The New England Journal of Medicine,” Vol. 333, No. 10, pp. 609-614 (Sept. 7, 1995)

Harris, et al. (Harris), "Nonsteroidal Antiinflammatory Drugs and Breast Cancer,” Epidemiology, Vol. 7, No. 2, pp. 203-205 (March 1996)

Munson et al. (Munson), Prevention, Vol. 48, No. 7, page 19-20 (July 1996)

The following reference is relied upon by this merits panel:

Kissel	5,861,170	Jan. 19, 1999

Ground of Rejection

Claims 27-36 stand rejected under 35 U.S.C. § 112, first paragraph, as being non-enabled by the specification. For the reasons discussed below, we affirm the rejection of claim 27-35, vacate the rejection of claim 36 and enter a new ground of rejection of claims 27-29 under the provisions of 37 CFR § 1.196(b).

Background

Appellants describe the invention at page 5 of the specification as being directed to a transdermal application system for the administration of acetylsalicylic acid or its pharmaceutical salts for antithrombotic therapy and prophylaxis against cancer. The system is described as avoiding the disadvantages associated with oral application and allows for target-specific dosages of the unchanged active substance.

Discussion

The rejection under 35 U.S.C. § 112, first paragraph

Claims 27-35:

As stated in Genentech Inc. v. Nova Nordisk A/S, 108 F.3d 1361, 1366, 42 USPQ2d 1001, 1005 (Fed. Cir. 1995):

> Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. See Brenner v. Manson, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.)

When the issue of enablement is raised under 35 U.S.C. § 112, first paragraph, the initial burden is on the Patent and Trademark Office to establish reasons why one skilled in the art would not believe the objective statements of enablement in the specification. In re Marzocchi, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971).

The examiner urges that (Answer, paragraph bridging pages 2-3):

> [t]he specification does not reasonably provide enablement for prevention of any and all cancers via transdermal administration of acetyl salicylic acid. The cancer therapy art remains highly unpredictable, and no examples exists for efficacy of a single compound or product against cancer generally. For example, certain cancers/tumors are dependent upon estrogen for their induction or stimulation (e.g. breast tumors) and others are not.

Thus, the issue presented in this appeal is whether the appellants' disclosure would have enabled one skilled in this art to use the claimed invention throughout its scope without undue experimentation.

Factors appropriate for determining whether undue experimentation is required to practice the claimed invention throughout its full scope are listed in In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). These factors include:

(1) the quantity of experimentation necessary,
(2) the amount of direction or guidance presented,
(3) the presence or absence of working examples,
(4) the nature of the invention,
(5) the state of the prior art,
(6) the relative skill of those in the art,
(7) the predictability or unpredictability of the art, and
(8) the breadth of the claims.

The examiner's rejection and the reasoning presented in support thereof focus on these factors. At pages 2 and 3 of the Answer, the examiner begins her analysis by interpreting the claims to encompass the use of the transdermal acetylsalicylic acid system for the prevention of cancers generally. The examiner urges that the prevention of cancer in general is a field of endeavor which remains unpredictable. The appellants argue that the examiner has failed to provide prior art documentation to justify the statement that the art area of cancer therapy remains highly unpredictable. However, the examiner's reasoning appears sound (Answer, paragraph bridging pages 2-3) and appellants have offered no meaningful evidence which would indicate that at the time of the filing of this application, the field of endeavor relating to the prevention of cancer, as compared to the treatment of patients with cancer, was not unpredictable. In such situations, it is not necessary to provide extrinsic evidence to establish the relevant factor. See Enzo Biochem. Inc. v. Calgene Inc., 188 F.3d 1362, 1371-72,

52 USPQ2d 1129, 1136 (Fed. Cir. 1999) ("We have also noted that all of the factors need not be reviewed when determining whether a disclosure is enabling.") (citing Amgen, Inc. v. Chugai Pharm. Co., Ltd. , 927 F.2d 1200, 1213, 18 USPQ2d 1016, 1027 (Fed. Cir. 1991)). The examiner, additionally, notes the lack of working examples describing the prevention of any kind of cancer by transdermal delivery of aspirin. (Answer, page 4). Further, the examiner notes that the claims are not limited to a particular type of cancer but are directed to the treatment of "cancer generally". (Answer, pages 3 and 4). The examiner concludes that (Answer, page 5):

> the instant specification does not provide enablement for the prevention of any cancer via the transdermal administration of aspirin, even at the disclosed blood levels.

As explained in PPG Indus., Inc. v. Guardian Indus. Corp., 75 F.3d 1558, 1564, 37 USPQ2d 1618, 1623 (Fed. Cir. 1996):

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed. Ex parte Jackson, 217 USPQ 804, 807 (Bd. App. 1982).

In the case before us, the examiner has established that the specification is lacking in guidance as to the use or application of the transdermal system for the prevention of cancers generally. Overall, we find that the examiner provides both evidence and sound scientific reasoning in support of her position. We, therefore, find no error in

the examiner's determination that a prima facie case of unpatentability has been established sufficient to support the rejections of claims 27-35 under 35 U.S.C. § 112, first paragraph. Having met her initial burden, the burden shifts to the appellants to rebut the basis for the rejection.

Appellants, initially, argue that the amount of direction or guidance present in the application is adequate for those skilled in this art to practice the invention and cites the article by Thun I, published in 1991, as evidence that aspirin has been shown to reduce the risk of colon cancer and reduce mortality caused by colonic cancer. (Principal Brief, paragraph bridging pages 7-8). However, as appellants acknowledge, the article is limited to the discussion of colon cancer and "fails to provide further information as to the manner and form of administration and dosage." (Principal Brief, page 8). Also, as pointed out by the examiner (Answer, page 4):

> In the article by Thun, it is clearly stated as a conclusion that "regular aspirin use at low dosages may (emphasis added) reduce the risk of fatal colon cancer. Whether this is due to a direct effect of aspirin . . . or to other factors is unclear." The results of this one study, are therefore, inconclusive as to the efficacy of aspirin in reducing the risk of fatal colon cancer, (sic, .) Moreover, however, even if aspirin was shown to be indisputably effective in reducing the risk of fatal colon cancer, that finding would not be predictive of aspirin preventing any and all cancers in general. Finally, "reducing the risk" is not equivalent to "prevention of".

We read Thun I to reflect caution on the part of the authors in describing the potential use of aspirin in the prevention of cancer in stating (page 1323, column 1, first full paragraph):

> The risk of all fatal cancers combined was somewhat lower among persons who used aspirin than in nonusers; this difference was of borderline statistical significance except in women in the highest category of use. No dose-response trend was seen for all cancers.

Thun I, also, states (page 1324, column 1, first paragraph):

> However, until the findings can be replicated, they should be interpreted cautiously, given the observational nature of our study and the important differences in the biology and epidemiology of these cancers.

Thus, appellants' evidence appears to urge caution with respect to the potential usefulness of aspirin in reducing the risk or prevention of cancer in a subject. In addition, the article provides little guidance which would assist those skilled in this art in practicing the presently claimed prevention of cancers in general and would not remove the need for experimentation to obtain the claimed prevention of cancer.

Appellants point to page 6, lines 22-25 of the present specification as disclosing that in the prophylaxis against cancer, a therapeutically effective amount of acetyl-salicylic acid and/or acetylsalicylic acid salts in the blood corresponds to blood level values of acetylsalicylic acid of between 0.1 and 1.0 µg/ml. (Principal Brief, page 11). The examiner acknowledges this disclosure, but urges that there are no working examples indicating prevention of any kind of cancer by transdermally delivering a sufficient quantity

of acetylsalicylic acid to provide blood levels between 0.1 to 1.0 microgram/ml. (Answer, page 4).

The appellants have, also, submitted 16 references, listed above, in addition to Thun I, to establish that aspirin has efficacy in the prevention of several different cancers. (Supplemental Reply Brief filed May 19, 1997). We note, initially, that all of these documents were published after the effective filing date of the present application. (December 12, 1992). Thus, they can not be said to represent the state of the art or the skill level of those in this art as of the filing date of this application. They are of little probative value for the proposition asserted by the appellants that the disclosure was sufficient at the time of filing of the application for patent to permit the practice of the invention without undue experimentation. In re Wright, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1514 (Fed. Cir. 1993) ("[A]ll of these developments occurred after the effective filing date of Wright's application and are of no significance regarding what one skilled in the art believed as of that date."). The examiner, having reviewed these documents, maintained the position that the evidence may link aspirin to a "reduction of risk" of cancer, but urges that this was not equivalent to "prevention" as presently claimed.

Having weighed all of the evidence of record, including the Wands factors, we find no error in the examiner's determination that the specification does not enable one skilled in this art to use the claimed invention throughout its scope without undue experimentation. Appellants have failed to provided evidence or arguments which, on balance, would be

sufficient to meet the burden of demonstrating that the disclosure is enabling. The examiner has established a prima facie case of lack of enablement which is sufficient to support the rejections of claims 27-35 under 35 U.S.C. § 112, first paragraph, which appellants have not overcome by arguments or convincing evidence. Therefore, the rejection of claims 27-35 under 35 U.S.C. § 112, first paragraph, is affirmed.

Claim 36:

We vacate the rejection of claim 36 under 35 U.S.C. § 112, first paragraph, as being based on a non-enabling disclosure for the following reasons. The record with regard to this claim is less than clear. Claim 36 is directed to a therapeutic method wherein the tumor prophylaxis is against tumor formation in the gastrointestinal tract. The appellants in their principal Appeal Brief at page 6 state that claims 27-36 are grouped together which is reasonably read as indicating that they stand and fall together. (37 CFR § 1.192(7)(1995)). Yet, in the Reply Brief of November 8, 1996 (Paper No. 18) at pages 1-2, appellants separately argue claim 36 as being limited to the use of aspirin against tumor formation in the gastrointestinal tract which reads on the use of aspirin to prevent colon cancer. The examiner acknowledged receipt and entry of the Reply Brief in a letter mailed November 26, 1996 (Paper No. 20),but failed to respond to the newly submitted arguments relating to claim 36. Thus, we are left with no rebuttal to arguments explicitly raised by the appellants and no indication whether these arguments taken with the teaching of the Thun I would reasonably be considered persuasive. In this regard, we note

the language at page 4 of the Answer where, in discussing the relevance of Thun I, the examiner states that "even if aspirin was shown to be indisputably effective in reducing the risk of fatal colon cancer, that finding would not be predictive of aspirin preventing any and all cancers in general." Since "indisputably effective" is not the test of whether the disclosure of the application is enabling for that which is claimed, the record is not clear as to the rejection of claim 36. For these reasons, we vacate the rejection of claim 36 under 35 U.S.C. § 112, first paragraph. On return of the application to the examining group, we would encourage the examiner to step back and consider the evidence of record, including the Thun I reference, and determine whether the facts and evidence would reasonably support the rejection of claim 36 under 35 U.S.C. § 112, first paragraph, using the factors set forth in Wands, supra.

New Ground of Rejection

Under the provisions of 37 CFR § 1.196(b) we enter the following new ground of rejection.

Claims 27-29 are rejected under 35 U.S.C. § 112, first paragraph, as failing to find adequate written description in the application as filed for the presently claimed invention. In pertinent part, claim 27 provides:

> said transdermal therapeutic application system comprising a matrix containing a substance such that hydrolysis of acetyl salicylic acid is precluded or at least greatly reduced; and said substance being selected from the group consisting of dioctyl cyclohexane, dioctyl cyclohexane dissolved in n-heptane,

> glycerol ester of a partially hydrogenated colophonium and dioctyl cyclohexane dissolved in n-heptane, and silicone oil.

This portion of claim 27 was added by amendment filed June 6, 1996 (Paper No. 15) to replace matter previously canceled.[3] Appellants indicate at page 2 of that paper, that "[t]he amendment to claim 27 is to insert the Markush group of substances that preclude or greatly reduce hydrolysis of acetyl salicylic acid." We find no written description, in the application as filed, of the members of the Markush group of claim 27 as being substances that preclude or greatly reduce hydrolysis of acetyl salicylic acid in the transdermal patch. The individual members of this group are named in the examples but there is no explicit statement of their function. We contrast this lack of description of these substances with the explicit statement at page 7 of the specification which states:

> For reducing or suppressing the hydrolysis, substances may be added such as acylating agents, preferably acetylating agents, and, in particular, acetic anhydride, . . .

Further, we compare claim 1 of co-assigned U.S. Patent 5,861,170 to Kissel wherein the members of the Markush group of claim 27 are designated as "solvents" rather than as hydrolysis suppressing agents. The members of the Markush group of claim 27 are

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[3] Similar terminology was initially added to claim 27 by amendment filed May 25, 1995 (Paper No. 7) in response to the first Office action. In the subsequent final rejection, the examiner rejected the claim as directed to subject matter which lacked antecedent basis in the application as filed for the description of the Markush group of substances as providing hydrophobic adjustments. This terminology was canceled from claim 27, as well as the other claims in which it appeared, by amendment filed April 8, 1996. (Paper No. 11). Claim 27 was subsequently amended at the time of the filing of the Appeal Brief to reintroduce the noted language. (Paper No. 15). While not explicitly stated in the record, the examiner's initials appear on this amendment authorizing entry thereof. Further, the Examiner's Answer, at page 2, indicates that the copy of the claims attached to the Appeal Brief, which included the cited language, was correct.

individually found in the examples at pages 10-13. In each of these examples, when acetylsalicylic acid is present, the exemplified composition additionally includes acetic anhydride which the specification describes as being the substance useful to preclude or at least reduce the hydrolysis of acetyl salicylic acid in the transdermal system. Thus, on these facts, the designation of the substances found in the Markush group of claim 27 as substances which preclude or at least greatly reduce hydrolysis lacks written support or antecedent basis in the application as filed.

Conclusion

The examiner's rejection of claims 27-35 under 35 U.S.C. § 112, first paragraph, is affirmed. The rejection of claim 36 under 35 U.S.C. § 112, first paragraph, is vacated. A new ground of rejection under 37 CFR § 1.196(b) is entered as to claims 27-29 under 35 U.S.C. § 112, first paragraph.

Time Period for Response

In addition to affirming the examiner’s rejection of one or more claims, this decision contains a new ground of rejection pursuant to 37 CFR § 1.196(b)(amended effective Dec. 1, 1997, by final rule notice, 62 Fed. Reg. 53,131, 53,197 (Oct. 10, 1997), 1203 Off. Gaz. Pat. & Trademark Office 63, 122 (Oct. 21, 1997)). 37 CFR § 1.196(b) provides, “A new ground of rejection shall not be considered final for purposes of judicial review.”

Regarding any affirmed rejection, 37 CFR § 1.197(b) provides:

> (b) Appellants may file a single request for rehearing within two months from the date of the original decision . . . .

37 CFR § 1.196(b) also provides that the appellant, WITHIN TWO MONTHS FROM THE DATE OF THE DECISION, must exercise one of the following two options with respect to the new ground of rejection to avoid termination of proceedings (37 CFR § 1.197(c)) as to the rejected claims:

> (1) Submit an appropriate amendment of the claims so rejected or a showing of facts relating to the claims so rejected, or both, and have the matter reconsidered by the examiner, in which event the application will be remanded to the examiner. . . .
>
> (2) Request that the application be reheard under § 1.197(b) by the Board of Patent Appeals and Interferences upon the same record. . . .

Should the appellants elect to prosecute further before the Primary Examiner pursuant to 37 CFR § 1.196(b)(1), in order to preserve the right to seek review under 35 U.S.C. §§ 141 or 145 with respect to the affirmed rejection, the effective date of the affirmance is deferred until conclusion of the prosecution before the examiner unless, as a mere incident to the limited prosecution, the affirmed rejection is overcome.

If the appellants elect prosecution before the examiner and this does not result in allowance of the application, abandonment or a second appeal, this case should be returned to the Board of Patent Appeals and Interferences for final action on the affirmed rejection, including any timely request for rehearing thereof.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

AFFIRMED-IN-PART

WILLIAM F. SMITH Administrative Patent Judge	)
FRED E. McKELVEY Senior Administrative Patent Judge	) BOARD OF PATENT) APPEALS AND) INTERFERENCES
DOUGLAS W. ROBINSON Administrative Patent Judge	)

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